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The Official Compendia of Standards

Volume 1

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USP U.S. PHARMACOPEIA
The Standard of Quality℠

2008

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THE UNITED STATES PHARMACOPEIA

NF 26

Volume 1

THE NATIONAL FORMULARY

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THE UNITED STATES PHARMACOPEIAL CONVENTION
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should be at least 25 mm wide. If the width of the strip is greater than 19 mm and not greater than 44 mm, the width of the jaws of the clamp should be at least 50 mm. If the width of the specimen is greater than 44 mm, cut a 25-mm strip, and use a clamp with jaws not less than 50 mm wide. Round all edges that might have a cutting action on the specimen to a radius of 0.4 mm. The jaws are 76.2 mm apart at the beginning of the test, and they separate at the rate of 30.5 cm ± 13 mm per minute. The machine is of such capacity that when the break occurs, the deviation of the pendulum from the vertical is between 9° and 45°.

⟨891⟩ THERMAL ANALYSIS

Precisely determined thermodynamic events, such as a change of state, can indicate the identity and purity of drugs. Compendial standards have long been established for the melting or boiling temperatures of substances. These transitions occur at characteristic temperatures, and the compendial standards therefore contribute to the identification of the substances. Because impurities affect these changes in predictable ways, the same compendial standards contribute to the control of the purity of the substances.

Thermal analysis in the broadest sense is the measurement of physical-chemical properties of materials as a function of temperature. Instrumental methods have largely supplanted older methods dependent on visual inspection and on measurements under fixed or arbitrary conditions, because they are objective, they provide more information, they afford permanent records, and they are generally more sensitive, more precise, and more accurate. Furthermore, they may provide information on crystal perfection, polymorphism, melting temperature, sublimation, glass transitions, dehydration, evaporation, pyrolysis, solid-solid interactions, and purity. Such data are useful in the characterization of substances with respect to compatibility, stability, packaging, and quality control. The measurements used most often in thermal analysis, i.e., transition temperature, thermogravimetry, and impurity analysis, are described here.

Transition Temperature—As a specimen is heated, its uptake (or evolution) of heat can be measured [differential scanning calorimetry (DSC)] or the resulting difference in temperature from that of an inert reference heated identically [differential thermal analysis (DTA)] can be measured. Either technique provides a record of the temperature at which phase changes, glass transitions, or chemical reactions occur. In the case of melting, both an "onset" and a "peak" temperature can be determined objectively and reproducibly, often to within a few tenths of a degree. While these temperatures are useful for characterizing substances, and the difference between the two temperatures is indicative of purity, the values cannot be correlated with subjective, visual "melting-range" values or with constants such as the triple point of the pure material.

A complete description of the conditions employed should accompany each thermogram, including make and model of instrument; record of last calibration; specimen size and identification (including previous thermal history); container; identity, flow rate, and pressure of gaseous atmosphere; direction and rate of temperature change; and instrument and recorder sensitivity.

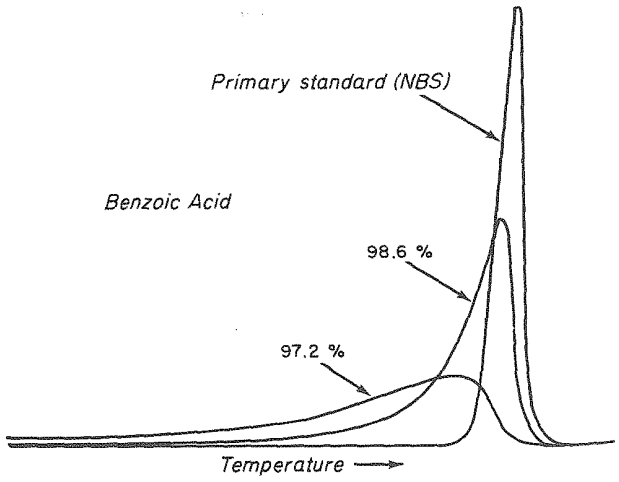
It is appropriate to make a preliminary examination over a wide range of temperature (typically room temperature to decomposition temperature or about 10° to 20° above the melting point) and over a wide range of heating rates (2° to 20° per minute), which may reveal unexpected effects; then a single examination or replicate examinations over a narrow range, bracketing the transition of interest at one or more lower heating rates, can be made. In examining pure crystalline materials, rates as low as 1° per minute may be appropriate, whereas rates of up to 10° per minute are more appropriate for polymeric and other semi-crystalline materials. As the reliability of the measurements varies from one substance to another, statements of the number of significant figures to be used in the reporting of intralaboratory repeatability and of interlaboratory reproducibility cannot be given here, but should be included in the individual monograph.

Thermogravimetric Analysis—Thermogravimetric analysis involves the determination of the mass of a specimen as a function of temperature, or time of heating, or both, and when properly applied, provides more useful information than does loss on drying at fixed temperature, often for a fixed time and in what is usually an ill-defined atmosphere. Usually, loss of surface-absorbed solvent can be distinguished from solvent in the crystal lattice and from degradation losses. The measurements can be carried out in atmospheres having controlled humidity and oxygen concentration to reveal interactions with the drug substance, between drug substances, and between active substances and excipients or packaging materials.

While the details depend on the manufacturer, the essential features of the equipment are a recording balance and a programmable heat source. Equipment differs in the ability to handle specimens of various sizes, the means of sensing specimen temperature, and the range of atmosphere control. Calibration is required with all systems, i.e., the mass scale is calibrated by the use of standard weights; calibration of the temperature scale, which is more difficult, involving either variations in positioning of thermocouples and their calibration; or in other systems, calibration involves the use of standard materials because it is assumed that the specimen temperature is the furnace temperature.

Procedural details are specified in order to provide for valid interlaboratory comparison of results. The specimen weight, source, and thermal history are noted. The equipment description covers dimensions and geometry, the materials of the test specimen holder, and the location of the temperature transducer. Alternatively, the make and model number of commercial equipment are specified. In all cases, the calibration record is specified. Data on the temperature environment include the initial and final temperatures and the rate of change or other details if nonlinear. The test atmosphere is critical; the volume, pressure, composition, whether static or dynamic, and if the latter, the flow rate and temperature are specified.

Eutectic Impurity Analysis—The basis of any calorimetric purity method is the relationship between the melting and freezing point depression, and the level of impurity. The melting of a compound is characterized by the absorption of latent heat of fusion, ΔH_f, at a specific temperature, T_o. In theory, a melting transition for an absolutely pure crystalline compound should occur within an infinitely narrow range. A broadening of the melting range, due to impurities, provides a sensitive criterion of purity. The effect is apparent visually by examination of thermograms of specimens differing by a few tenths percent in impurity content. A material that is 99% pure is about 20% molten at 3° below the melting point of the pure material (see *accompanying figure*).



Superimposed Thermograms Illustrating the Effect of Impurities on DSC Melting Peak Shape

The parameters of melting (melting range, ΔH_f, and calculated eutectic purity) are readily obtained from the thermogram of a single melting event using a small test specimen, and the method does not require multiple, precise actual temperature measurements. Thermogram units are directly convertible to heat transfer, millicalories per second.

The lowering of the freezing point in *dilute solutions* by molecules of nearly equal size is expressed by a modified van't Hoff equation:

$$\frac{dT}{dX_2} = \frac{RT^2}{\Delta H_f} \cdot (K - 1), \qquad (1)$$

in which T= absolute temperature in degrees Kelvin (°K), X_2 = mole fraction of minor component (solute; impurity), ΔH_f = molar heat of fusion of the major component, R = gas constant, and K = distribution ratio of solute between the solid and liquid phases.

Assuming that the temperature range is small and that no solid solutions are formed ($K = 0$), integration of the van't Hoff equation yields the following relationship between mole fraction of impurity and the melting-point depression:

$$X_2 = \frac{(T_o - T_m)\Delta H_f}{RT_o^2}, \qquad (2)$$

in which T_o= melting point of the pure compound, in °K, and T_m = melting point of the test specimen, in °K.

With no solid solution formation, the concentration of impurity in the liquid phase at any temperature during the melting is inversely proportional to the fraction melted at that temperature, and the melting-point depression is directly proportional to the mole fraction of impurity. A plot of the observed test specimen temperature, T_s, versus the reciprocal of the fraction melted, $1/F$, at temperature T_s, should yield a straight line with the slope equal to the melting-point depression ($T_o - T_m$). The theoretical melting point of the pure compound is obtained by extrapolation to $1/F = 0$:

$$T_s = T_o - \frac{RT_o^2 X_2 (1/F)}{\Delta H_f}. \qquad (3)$$

Substituting the experimentally obtained values for $T_o - T_m$, ΔH_f, and T_o in *Equation 2* yields the mole fraction of the total eutectic impurity, which, when multiplied by 100, gives the mole percentage of total eutectic impurities.

Deviations from the theoretical linear plot also may be due to solid solution formation ($K \neq 0$), so that care must be taken in interpreting the data.

To observe the linear effect of the impurity concentration on the melting-point depression, the impurity must be *soluble* in the liquid phase or melt of the compound, but *insoluble* in the solid phase, i.e., no solid solutions are formed. Some chemical similarities are necessary for solubility in the melt. For example, the presence of ionic compounds in neutral organic compounds and the occurrence of thermal decomposition may not be reflected in purity estimates. The extent of these theoretical limitations has been only partially explored.

Impurities present from the synthetic route often are similar to the end product, hence there usually is no problem of solubility in the melt. Impurities consisting of molecules of the same shape, size, and character as those of the major component can fit into the matrix of the major component without disruption of the lattice, forming solid solutions or inclusions; such impurities are not detectable by DSC. Purity estimates are too high in such cases. This is more common with less-ordered crystals as indicated by low heats of fusion.

Impurity levels calculated from thermograms are reproducible and probably reliable within 0.1% for ideal compounds. Melting-point determinations by scanning calorimetry have a reproducibility with a standard deviation of about 0.2°. Calibration against standards may allow about 1° accuracy for the melting point, so that this technique is comparable to other procedures.

Compounds that exist in polymorphic form cannot be used in purity determination unless the compound is completely converted to one form. On the other hand, DSC and DTA are inherently useful for detecting, and therefore monitoring, polymorphism.

Procedure—The actual procedure and the calculations to be employed are dependent on the particular instrument used. Consult the manufacturer's literature and/or the thermal analysis literature for the most appropriate technique for a given instrument. In any event, it is imperative to keep in mind the limitations of solid solution formation, insolubility in the melt, polymorphism, and decomposition during the analysis.

⟨905⟩ UNIFORMITY OF DOSAGE UNITS

[NOTE—In this chapter, *unit* and *dosage unit* are synonymous.]

To ensure the consistency of dosage units, each unit in a batch should have a drug substance content within a narrow range around the label claim. Dosage units are defined as dosage forms containing a single dose or a part of a dose of drug substance in each unit. The uniformity of dosage units specification is not intended to apply to suspensions, emulsions, or gels in unit-dose containers intended for topical administration.

The term "uniformity of dosage unit" is defined as the degree of uniformity in the amount of the drug substance among dosage units. Therefore, the requirements of this chapter apply to each drug substance being comprised in dosage units containing one or more drug substances, unless otherwise specified in the individual monograph.

The uniformity of dosage units can be demonstrated by either of two methods, *Content Uniformity* or *Weight Variation* (see *Table 1*). The test for *Content Uniformity* is based on the assay of the individual content of drug substance(s) in a number of individual dosage units to determine whether the individual content is within the limits set. The *Content Uniformity* method may be applied in all cases. The test for *Content Uniformity* is required for those dosage forms described in *(C1)–(C6)* below:

(C1) coated tablets, other than film-coated tablets containing 25 mg or more of a drug substance that comprises 25% or more (by weight) of one tablet;

(C2) transdermal systems;

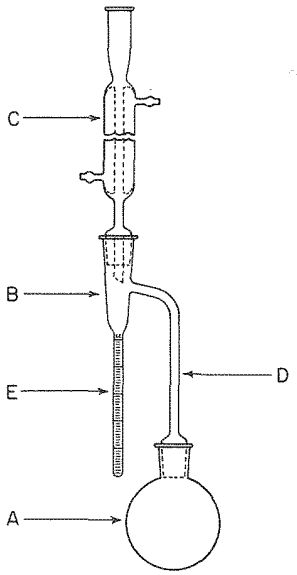
(C3) suspensions or emulsions or gels in single-unit containers or in soft capsules that are intended for systemic administration only (not for those drug products that are intended for topical administration);

(C4) inhalations (other than solutions for inhalation packaged in glass or plastic ampuls and intended for use in nebulizers) packaged in premetered dosage units. For inhalers and premetered dosage units labeled for use with a named inhalation device, also see *Aerosols, Nasal Sprays, Metered-Dose Inhalers, and Dry Powder Inhalers* ⟨601⟩;

(C5) solids (including sterile solids) that are packaged in single-unit containers and that contain active or inactive added substances, except that the test for *Weight Variation* may be applied in the special cases stated in *(W3)* below; and

(C6) suppositories.

The test for *Weight Variation* is applicable for the following dosage forms:



Toluene Moisture Apparatus

The critical dimensions of the parts of the apparatus are as follows. The connecting tube *D* is 9 to 11 mm in internal diameter. The trap is 235 to 240 mm in length. The condenser, if of the straight-tube type, is approximately 400 mm in length and not less than 8 mm in bore diameter. The receiving tube *E* has a 5-mL capacity, and its cylindrical portion, 146 to 156 mm in length, is graduated in 0.1-mL subdivisions, so that the error of reading is not greater than 0.05 mL for any indicated volume. The source of heat is preferably an electric heater with rheostat control or an oil bath. The upper portion of the flask and the connecting tube may be insulated.

Clean the receiving tube and the condenser with chromic acid cleansing mixture, thoroughly rinse with water, and dry in an oven. Prepare the toluene to be used by first shaking with a small quantity of water, separating the excess water, and distilling the toluene.

Procedure—Place in the dry flask a quantity of the substance, weighed accurately to the nearest centigram, which is expected to yield 2 to 4 mL of water. If the substance is of a pasty character, weigh it in a boat of metal foil of a size that will just pass through the neck of the flask. If the substance is likely to cause bumping, add enough dry, washed sand to cover the bottom of the flask, or a number of capillary melting-point tubes, about 100 mm in length, sealed at the upper end. Place about 200 mL of toluene in the flask, connect the apparatus, and fill the receiving tube *E* with toluene poured through the top of the condenser. Heat the flask gently for 15 minutes and, when the toluene begins to boil, distill at the rate of about 2 drops per second until most of the water has passed over, then increase the rate of distillation to about 4 drops per second. When the water has apparently all distilled over, rinse the inside of the condenser tube with toluene while brushing down the tube with a tube brush attached to a copper wire and saturated with toluene. Continue the distillation for 5 minutes, then remove the heat, and allow the receiving tube to cool to room temperature. If any droplets of water adhere to the walls of the receiving tube, scrub them down with a brush consisting of a rubber band wrapped around a copper wire and wetted with toluene. When the water and toluene have separated completely, read the volume of water, and calculate the percentage that was present in the substance.

METHOD III (GRAVIMETRIC)

Procedure for Chemicals—Proceed as directed in the individual monograph preparing the chemical as directed under *Loss on Drying* ⟨731⟩.

Procedure for Biologics—Proceed as directed in the individual monograph.

Procedure for Articles of Botanical Origin—Place about 10 g of the drug, prepared as directed (see *Methods of Analysis* under *Articles of Botanical Origin* ⟨561⟩) and accurately weighed, in a tared evaporating dish. Dry at 105° for 5 hours, and weigh. Continue the drying and weighing at 1-hour intervals until the difference between two successive weighings corresponds to not more than 0.25%.

⟨941⟩ X-RAY DIFFRACTION

Every crystal form of a compound produces its own characteristic X-ray diffraction pattern. These diffraction patterns can be derived either from a single crystal or from a powdered specimen (containing numerous crystals) of the material. The spacings between and the relative intensities of the diffracted maxima can be used for qualitative and quantitative analysis of crystalline materials. Powder diffraction techniques are most commonly employed for routine identification and the determination of relative purity of crystalline materials. Small amounts of impurity, however, are not normally detectable by the X-ray diffraction method, and for quantitative measurements it is necessary to prepare the sample carefully to avoid preferred orientation effects.

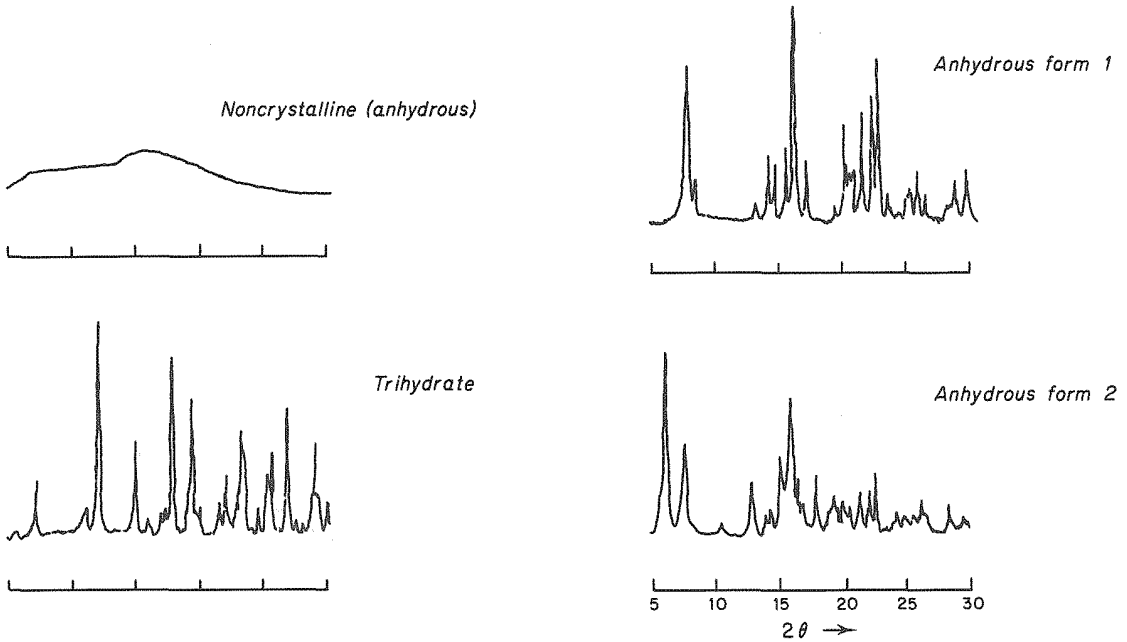
The powder methods provide an advantage over other means of analysis in that they are usually nondestructive in nature (specimen preparation is usually limited to grinding to ensure a randomly oriented sample, and deleterious effects of X-rays on solid pharmaceutical compounds are not commonly encountered). The principal use of single-crystal diffraction data is for the determination of molecular weights and analysis of crystal structures at the atomic level. However, diffraction established for a single crystal can be used to support a specific powder pattern as being truly representative of a single phase.

Solids—A solid substance can be classified as being crystalline, noncrystalline, or a mixture of the two forms. In crystalline materials, the molecular or atomic species are ordered in a three-dimensional array, called a lattice, within the solid particles. This ordering of molecular components is lacking in noncrystalline material. Noncrystalline solids sometimes are referred to as glasses or amorphous solids when repetitive order is nonexistent in all three dimensions. It is also possible for order to exist in only one or two dimensions, resulting in mesomorphic phases (liquid crystals). Although crystalline materials are usually considered to have well-defined visible external morphologies (their habits), this is not a necessity for X-ray diffraction analysis.

The relatively random arrangement of molecules in noncrystalline substances makes them poor coherent scatterers of X-rays, resulting in broad, diffuse maxima in diffraction patterns. Their X-ray patterns are quite distinguishable from crystalline specimens, which give sharply defined diffraction patterns.

Many compounds are capable of crystallizing in more than one type of crystal lattice. At any particular temperature and pressure, only one crystalline form (polymorph) is thermodynamically stable. Since the rate of phase transformation of a metastable polymorph to the stable one can be quite slow, it is not uncommon to find several polymorphs of crystalline pharmaceutical compounds existing under normal handling conditions.

In addition to exhibiting polymorphism, many compounds form crystalline solvates in which the solvent molecule is an integral part of the crystal structure. Just as every polymorph has its own characteristic X-ray patterns, so does every solvate. Sometimes the differences in the diffraction patterns of different polymorphs are relatively minor, and must be very carefully evaluated before a definitive conclusion is reached. In some instances, these polymorphs and/or solvates show varying dissolution rates. Therefore, on the time scale of pharmaceutical bioavailability, different total amounts of drug are dissolved, resulting in potential bioinequivalence of the several forms of the drug.



Typical Powder Patterns Obtained for Four Solid Phases of Ampicillin

Fundamental Principles—A collimated beam of monochromatic X-rays is diffracted in various directions when it impinges upon a rotating crystal or randomly oriented powdered crystal. The crystal acts as a three-dimensional diffraction grating to this radiation. This phenomenon is described by Braggs law, which states that diffraction (constructive interference) can occur only when waves that are scattered from different regions of the crystal, in a specific direction, travel distances differing by integral numbers (n) of the wavelength (λ). Under such circumstances, the waves are in phase. This condition is described by the Braggs equation:

$$\frac{n\lambda}{2 \sin \theta} = d_{hkl},$$

in which d_{hkl} denotes the interplanar spacings and θ is the angle of diffraction.

A family of planes in space can be indexed by three whole numbers, usually referred to as Miller indices. These indices are the reciprocals, reduced to smallest integers, of the intercepts that a plane makes along the axes corresponding to three nonparallel edges of the unit cell (basic crystallographic unit). The unit cell dimensions are given by the lengths of the spacings along the three axes, a, b, c, and the angles between them, α, β, and γ. The interplanar spacing for a specific set of parallel planes hkl is denoted by d_{hkl}. Each such family of planes may show higher orders of diffraction where the d values for the related families of planes nh, nk, nl are diminished by the factor $1/n$ (n being an integer: 2, 3, 4, etc.). Every set of planes throughout a crystal has a corresponding Braggs diffraction angle associated with it (for a specific λ).

The amplitude of a diffracted X-ray beam from any set of planes is dependent upon the following atomic properties of the crystal: (1) position of each atom in the unit cell; (2) the respective atomic scattering factors; and (3) the individual thermal motions. Other factors that directly influence the intensities of the diffracted beam are: (1) the intensity and wavelength of the incident radiation; (2) the volume of crystalline specimen; (3) the absorption of the X-radiation by the specimen; and (4) the experimental arrangement utilized to record the intensity data. Thus, the experimental conditions are especially important for measurement of diffraction intensities.

Only a limited number of Braggs planes are in a position to diffract when monochromatized X-rays pass through a single crystal. Techniques of recording the intensities of all of the possible diffracting hkl planes involve motion of the single crystal and the recording media. Recording of these data is accomplished by photographic techniques (film) or with radiation detectors.

A beam passing through a very large number of small, randomly oriented crystals produces continuous cones of diffracted rays from each set of lattice planes. Each cone corresponds to the diffraction from various planes having a similar interplanar spacing. The intensities of these Braggs reflections are recorded by either film or radiation detectors. The Braggs angle can be measured easily from a film, but the advent of radiation detectors has made possible the construction of diffractometers that read this angle directly. The intensities and d spacings are more conveniently determined with powder diffractometers employing radiation detectors than by film methods. Microphotometers are frequently used for precise intensity measurements of films.

An example of the type of powder patterns obtained for four different solid phases of ampicillin are shown in the *accompanying figure*. These diffraction patterns were derived from a powder diffractometer equipped with a Geiger-Müller detector; nickel-filtered Cu $K\alpha$ radiation was used.

Radiation—The principal radiation sources utilized for X-ray diffraction are vacuum tubes utilizing copper, molybdenum, iron, and chromium as anodes; copper X-rays are employed most commonly for organic substances. For each of these radiations there is an element that will filter off the $K\beta$ radiation and permit the $K\alpha$ radiation to pass (nickel is used, in the case of copper radiation). In this manner the radiation is practically monochromatized. The choice of radiation to be used depends upon the absorption characteristics of the material and possible fluorescence by atoms present in the specimen.

Caution—Care must be taken in the use of such radiation. Those not familiar with the use of X-ray equipment should seek expert advice. Improper use can result in harmful effects to the operator.

Test Preparation—In an attempt to improve randomness in the orientation of crystallites (and, for film techniques, to avoid a grainy pattern), the specimen may be ground in a mortar to a fine powder. Grinding pressure has been known to induce phase transformations; therefore, it is advisable to check the diffraction pattern of the unground sample.

In general, the shapes of many crystalline particles tend to give a specimen that exhibits some degree of preferred orientation in the specimen holder. This is especially evident for needle-like or plate-like crystals where size reduction yields finer needles or platelets. Preferred orientation in the specimen influences the relative intensities of various reflections.

Several specialized handling techniques may be employed to minimize preferred orientation, but further reduction of particle size is often the best approach.

Where very accurate measurement of the Braggs angles is necessary, a small amount of an internal standard can be mixed into the specimen. This enables the film or recorder tracing to be calibrated. If comparisons to literature values (including compendial limits) of *d* are being made, calibrate the diffractometer. NIST standards are available covering to a *d*-value of 0.998 nm. Tetradecanol[1] may be used (*d* is 3.963 nm) for larger spacing.

The absorption of the radiation by any specimen is determined by the number and kinds of atoms through which the X-ray beam passes. An organic matrix usually absorbs less of the diffracted radiation than does an inorganic matrix. Therefore, it is important in quantitative studies that standard curves relating amount of material to the intensity of certain *d* spacings for that substance be determined in a matrix similar to that in which the substance will be analyzed.

In quantitative analyses of materials, a known amount of standard usually is added to a weighed amount of specimen to be analyzed. This enables the amount of the substance to be determined relative to the amount of standard added. The standard used should have approximately the same density as the specimen and similar absorption characteristics. More important, its diffraction pattern should not overlap to any extent with that of the material to be analyzed. Under these conditions a linear relationship between line intensity and concentration exists. In favorable cases, amounts of crystalline materials as small as 10% may be determined in solid matrices.

Identification of crystalline materials can be accomplished by comparison of X-ray powder diffraction patterns obtained for known[2] materials with those of the unknown. The intensity ratio (ratio of the peak intensity of a particular *d* spacing to the intensity of the strongest maxima in the diffraction pattern) and the *d* spacing are used in the comparison. If a reference material (e.g., USP Reference Standard) is available, it is preferable to generate a primary reference pattern on the same equipment used for running the unknown sample, and under the same conditions. For most organic crystals, it is appropriate to record the diffraction pattern to include values for 2θ that range from as near zero degrees as possible to 40 degrees. Agreement between sample and reference should be within the calibrated precision of the diffractometer for diffraction angle (2θ values should typically be reproducible to ±0.10 degrees), while relative intensities between sample and reference may vary considerably. For other types of samples (e.g., inorganic salts), it may be necessary to extend the 2θ region scanned to well beyond 40 degrees. It is generally sufficient to scan past the ten strongest reflections identified in the Powder Diffraction File.[2]

[1] Brindley, GW and Brown, G, eds., *Crystal Structures of Clay Minerals and Their X-ray Identification*, Mineralogical Society Monograph No. 5, London, 1980, pp. 318 ff.
[2] The International Centre for Diffraction Data, Newtown Square Corporate Campus, 12 Campus Boulevard, Newtown Square, PA 19073, maintains a file on more than 60,000 crystalline materials, both organic and inorganic, suitable for such comparisons.

Suspensions

Ophthalmic suspensions are sterile liquid preparations containing solid particles dispersed in a liquid vehicle intended for application to the eye (see *Suspensions*). It is imperative that such suspensions contain the drug in a micronized form to prevent irritation and/or scratching of the cornea. Ophthalmic suspensions should never be dispensed if there is evidence of caking or aggregation.

Strips

Fluorescein sodium solution should be dispensed in a sterile, single-use container or in the form of a sterile, impregnated paper strip. The strip releases a sufficient amount of the drug for diagnostic purposes when touched to the eye being examined for a foreign body or a corneal abrasion. Contact of the paper with the eye may be avoided by leaching the drug from the strip onto the eye with the aid of sterile water or sterile sodium chloride solution.

PASTES

Pastes are semisolid dosage forms that contain one or more drug substances intended for topical application. One class is made from a single-phase aqueous gel (e.g., *Carboxymethylcellulose Sodium Paste*). The other class, the fatty pastes (e.g., *Zinc Oxide Paste*), consists of thick, stiff ointments that do not ordinarily flow at body temperature, and therefore serve as protective coatings over the areas to which they are applied.

The fatty pastes appear less greasy and more absorptive than ointments by reason of a high proportion of drug substance(s) having an affinity for water. These pastes tend to absorb serous secretions, and are less penetrating and less macerating than ointments, so that they are preferred for acute lesions that have a tendency towards crusting, vesiculation, or oozing.

A dental paste is intended for adhesion to the mucous membrane for local effect (e.g., *Triamcinolone Acetonide Dental Paste*). Some paste preparations intended for administration to animals are applied orally. The paste is squeezed into the mouth of the animal, generally at the back of the tongue, or is spread inside the mouth.

PELLETS

See *Implants*.

POWDERS

Powders are intimate mixtures of dry, finely divided drugs and/or chemicals that may be intended for internal (Oral Powders) or external (Topical Powders) use. Because of their greater specific surface area, powders disperse and dissolve more readily than compacted dosage forms. Children and those adults who experience difficulty in swallowing tablets or capsules may find powders more acceptable. Drugs that are too bulky to be formed into tablets or capsules of convenient size may be administered as powders. Immediately prior to use, oral powders are mixed in a beverage or apple sauce.

Often, stability problems encountered in liquid dosage forms are avoided in powdered dosage forms. Drugs that are unstable in aqueous suspensions or solutions may be prepared in the form of granules or powders. These are intended to be constituted by the pharmacist by the addition of a specified quantity of water just prior to dispensing. Because these constituted products have limited stability, they are required to have a specified expiration date after constitution and may require storage in a refrigerator.

Oral powders may be dispensed in doses premeasured by the pharmacist, i.e., divided powders, or in bulk. Traditionally, divided powders have been wrapped in materials such as bond paper and parchment. However, the pharmacist may provide greater protection from the environment by sealing individual doses in small cellophane or polyethylene envelopes.

Granules for veterinary use may be administered by sprinkling the dry powder on animal feed or by mixing it with animal food.

Bulk oral powders are limited to relatively nonpotent drugs such as laxatives, antacids, dietary supplements, and certain analgesics that the patient may safely measure by the teaspoonful or capful. Other bulky powders include douche powders, tooth powders, and dusting powders. Bulk powders are best dispensed in tight, wide-mouth glass containers to afford maximum protection from the atmosphere and to prevent the loss of volatile constituents.

Dusting powders are impalpable powders intended for topical application. They may be dispensed in sifter-top containers to facilitate dusting onto the skin. In general, dusting powders should be passed through at least a 100-mesh sieve to assure freedom from grit that could irritate traumatized areas (see *Powder Fineness* ⟨811⟩).

PREMIXES

Premixes are mixtures of one or more drug substances with suitable vehicles. Premixes are intended for admixture to animal feedstuffs before administration. They are used to facilitate dilution of the active drug components with animal feed. Premixes should be as homogeneous as possible. It is essential that materials of suitable fineness be used and that thorough mixing be achieved at all stages of premix preparation. Premixes may be prepared as powder, pellets, or in granulated form. The granulated form is free-flowing and free from aggregates.

SOLUTIONS

Solutions are liquid preparations that contain one or more chemical substances dissolved, i.e., molecularly dispersed, in a suitable solvent or mixture of mutually miscible solvents. Since molecules in solutions are uniformly dispersed, the use of solutions as dosage forms generally provides for the assurance of uniform dosage upon administration, and good accuracy when diluting or otherwise mixing solutions.

Substances in solutions, however, are more susceptible to chemical instability than the solid state and dose for dose, generally require more bulk and weight in packaging relative to solid dosage forms. For all solutions, but particularly those containing volatile solvents, tight containers, stored away from excessive heat, should be used. Consideration should also be given to the use of light-resistant containers when photolytic chemical degradation is a potential stability problem. Dosage forms categorized as "Solutions" are classified according to route of administration, such as "Oral Solutions" and "Topical Solutions," or by their solute and solvent systems, such as "Spirits," "Tinctures," and "Waters." Solutions intended for parenteral administration are officially entitled "Injections" (see *Injections* ⟨1⟩).

Oral Solutions

Oral Solutions are liquid preparations, intended for oral administration, that contain one or more substances with or without flavoring, sweetening, or coloring agents dissolved in water or cosolvent-water mixtures. Oral Solutions may be formulated for direct oral administration to the patient or they may be dispensed in a more concentrated form that must be diluted prior to administration. It is important to recognize that dilution with water of Oral Solutions containing cosolvents, such as alcohol, could lead to precipitation of some ingredients. Hence, great care must be taken in diluting concentrated solutions when cosolvents are present. Preparations dispensed as soluble solids or soluble mixtures of solids, with the intent of dissolving them in a solvent and administering them orally, are designated "for Oral Solution" (e.g., *Potassium Chloride for Oral Solution*).

Oral Solutions containing high concentrations of sucrose or other sugars traditionally have been designated as Syrups. A near-saturated solution of sucrose in purified water, for example, is known as Syrup or "Simple Syrup." Through common usage the term, syrup, also has been used to include any other liquid dosage form prepared in a sweet and viscid vehicle, including oral suspensions.

medicaments such as chloral hydrate and phenol to soften the base. It is important that the finished suppository melt at body temperature.

The approximate weights of suppositories prepared with cocoa butter are given below. Suppositories prepared from other bases vary in weight and generally are heavier than the weights indicated here.

Rectal Suppositories for adults are tapered at one or both ends and usually weigh about 2 g each.

Vaginal Suppositories are usually globular or oviform and weigh about 5 g each. They are made from water-soluble or water-miscible vehicles such as polyethylene glycol or glycerinated gelatin.

Suppositories with cocoa butter base require storage in well-closed containers, preferably at a temperature below 30° (controlled room temperature).

Cocoa Butter Substitutes

Fat-type suppository bases can be produced from a variety of vegetable oils, such as coconut or palm kernel, which are modified by esterification, hydrogenation, and fractionation to obtain products of varying composition and melting temperatures (e.g., *Hydrogenated Vegetable Oil* and *Hard Fat*). These products can be so designed as to reduce rancidity. At the same time, desired characteristics such as narrow intervals between melting and solidification temperatures, and melting ranges to accommodate various formulation and climatic conditions, can be built in.

Glycerinated Gelatin Suppositories

Medicinal substances may be incorporated into glycerinated gelatin bases by addition of the prescribed quantities to a vehicle consisting of about 70 parts of glycerin, 20 parts of gelatin, and 10 parts of water.

Glycerinated gelatin suppositories require storage in tight containers, preferably at a temperature below 35°.

Polyethylene Glycol–Base Suppositories

Several combinations of polyethylene glycols having melting temperatures that are above body temperature have been used as suppository bases. Inasmuch as release from these bases depends on dissolution rather than on melting, there are significantly fewer problems in preparation and storage than exist with melting-type vehicles. However, high concentrations of higher-molecular-weight polyethylene glycols may lengthen dissolution time, resulting in problems with retention. Labels on polyethylene glycol suppositories should contain directions that they be moistened with water before inserting. Although they can be stored without refrigeration, they should be packaged in tightly closed containers.

Surfactant Suppository Bases

Several nonionic surface-active agents closely related chemically to the polyethylene glycols can be used as suppository vehicles. Examples of such surfactants are polyoxyethylene sorbitan fatty acid esters and the polyoxyethylene stearates. These surfactants are used alone or in combination with other suppository vehicles to yield a wide range of melting temperatures and consistencies. One of the major advantages of such vehicles is their water-dispersibility. However, care must be taken with the use of surfactants, because they may either increase the rate of drug absorption or interact with drug molecules, causing a decrease in therapeutic activity.

Tableted Suppositories or Inserts

Vaginal suppositories occasionally are prepared by the compression of powdered materials into a suitable shape. They are prepared also by encapsulation in soft gelatin.

SUSPENSIONS

Suspensions are liquid preparations that consist of solid particles dispersed throughout a liquid phase in which the particles are not soluble. Dosage forms officially categorized as "Suspensions" are designated as such if they are not included in other more specific categories of suspensions, such as Oral Suspensions, Topical Suspensions, etc. (see these other categories). Some suspensions are prepared and ready for use, while others are prepared as solid mixtures intended for constitution just before use with an appropriate vehicle. Such products are designated "for Oral Suspension", etc. The term "Milk" is sometimes used for suspensions in aqueous vehicles intended for oral administration (e.g., *Milk of Magnesia*). The term "Magma" is often used to describe suspensions of inorganic solids such as clays in water, where there is a tendency for strong hydration and aggregation of the solid, giving rise to gel-like consistency and thixotropic rheological behavior (e.g., *Bentonite Magma*). The term "Lotion" has been used to categorize many topical suspensions and emulsions intended for application to the skin (e.g., *Calamine Lotion*). Some suspensions are prepared in sterile form and are used as Injectables, as well as for ophthalmic and otic administration. These may be of two types, ready to use or intended for constitution with a prescribed amount of Water for Injection or other suitable diluent before use by the designated route. Suspensions should not be injected intravenously or intrathecally.

Suspensions intended for any route of administration should contain suitable antimicrobial agents to protect against bacteria, yeast, and mold contamination (see *Emulsions* for some consideration of antimicrobial preservative properties that apply also to Suspensions). By its very nature, the particular matter in a suspension may settle or sediment to the bottom of the container upon standing. Such sedimentation may also lead to caking and solidification of the sediment with a resulting difficulty in redispersing the suspension upon agitation. To prevent such problems, suitable ingredients that increase viscosity and the gel state of the suspension, such as clays, surfactants, polyols, polymers, or sugars, should be added. It is important that suspensions always be shaken well before use to ensure uniform distribution of the solid in the vehicle, thereby ensuring uniform and proper dosage. Suspensions require storage in tight containers.

Oral Suspensions

Oral Suspensions are liquid preparations containing solid particles dispersed in a liquid vehicle, with suitable flavoring agents, intended for oral administration. Some suspensions labeled as "Milks" or "Magmas" fall into this category.

Topical Suspensions

Topical Suspensions are liquid preparations containing solid particles dispersed in a liquid vehicle, intended for application to the skin. Some suspensions labeled as "Lotions" fall into this category.

Otic Suspensions

Otic Suspensions are liquid preparations containing micronized particles intended for instillation in the outer ear.

Ophthalmic Suspensions

See *Ophthalmic Preparations*.

SYRUPS

See *Oral Solutions*.